Program Announcements (PA'S)

RESEARCH ON BONE ACTIVE HORMONES AND CYTOKINES

NIH Guide - Volume 15, Number 27, November. 28, 1986

PA NUMBER: PA-87-05

P.T. 34; K.W. 0785050, 1002004, 0765030, 0760025, 0760020, 0705050

National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite investigator-initiated research grant applications to: 1) develop better in vitro systems in which to study the effects of hormones, hormone analogs, cell-derived growth factors or cytokines, and other drugs or factors which regulate bone metabolism; 2) define the factors which regulate bone formation and remodeling; and 3) study synergism and antagonism among these factors.

DISCIPLINES AND EXPERTISE

Interdisciplinary approaches may be needed for this study with expertise required in several of the following areas: endocrinology, cell biology, mineral metabolism, mechanism of hormone action, and peptide and/or steroid biochemistry.

BACKGROUND

Hormones, including parathyroid hormone, the calciferol, calcitonin, steroids, and somatomedins, are major regulators of bone formation, remodeling, structure, and function. The role of these systemic hormones in maintenance of skeletal integrity and calcium and phosphate homeostasis is well established. Conditions of hormone excess or deficiency frequently are manifested through the skeletal system. Hormones and their analogs are often used as therapeutic agents in skeletal diseases. However, information on the mechanism by which these hormones act on bone is quite limited and much of our knowledge about their role in bone metabolism is descriptive.

Recently, a number of local growth factors, or cytokines, have been identified which may play a role in regulation of bone metabolism. These cell-derived factors are synthesized by leukocytes,fibroblasts, osteoblasts and other cell types. These factors include, but are not limited to, bone derived growth factors, cartilage derived growth factor, human skeletal growth factor, human platelet derived growth factor, human and transforming growth factors, epidermal growth factor, tumor necrosis factors, interleukins, interferon, and relaxin. Some of these factors are produced by normal cells and may regulate the normal processes of bone metabolism. Others are produced by human or animal tumors and may mediate the pathological bone resorption and hypercalcemia associated with cancer. The possible role of these local growth factors in mediating the effects of systemic hormones remains to be determined.

Many of the unresolved issues of clinical relevance concerning the effects of hormones or cytokines on the skeletal system can best be answered using in vitro systems in which confounding variables can be controlled. Recent advances in development of growth systems for bone cells, such as the use of fibronectin or collagen coating of growth surfaces, make possible studies of several months duration. However, much work remains to be done to develop in vitro systems suitable for investigating the effects of bone active hormones and of the newly described bone active cytokines.

OBJECTIVES

This solicitation is intended to stimulate research that will result in the development of new or improved in vitro systems in which to study the effects of the hormones and cytokines which effect bone metabolism. It is also intended to stimulate investigation utilizing new or existing in vitro systems of the mechanism of action and interactions of hormones and cytokines known to regulate bone metabolism and to identify other potential bone active agents.

SCOPE

Some examples of research topics which would be considered responsive to this solicitation include the following:

* development of new or improved in vitro bone resorbing and bone forming systems such as fetal calvaria, rat long bones with enhanced release of radiolabeled calcium and decreased collagen synthesis, or other appropriate systems.

* development of new or improved in vitro bone forming and bone resorbing cell lines from animal and human sources utilizing serum free media whenever possible. Purity and phenotypic stability of cells should be emphasized.

* development of pure preparations of bone cells per se prepared from embryonic bone tumor lines.

* testing in new or existing in vitro systems of the established bone active hormones and the newly described bone active cytokines to elucidate their mechanism of action.

* determination in in vitro systems of whether a given hormone or analog results in catabolic or anabolic effects on bone and/or a determination of whether the effect produced depends on the type of bone being examined (i.e., embryonic or mature bone) or the hormone concentration.

* investigate in an in vitro system of the long-term effects of hormones or cytokines in terms of parameters such as cystolic calcium accumulation, cell growth, and cell differentiation.

* in vitro studies to define whether skeletal effects of hormones occur as a result of direct action of the hormone on bone or whether they are mediated through other factors.

* identification of factors such as bone derived growth factor and human skeletal growth factor which are produced locally by bone cells and investigation of the role of systemic hormones and other factors in the regulation of their production.

* in vitro studies to define whether skeletal effects of hormones occur as a result of direct action of the hormone on bone or whether they are mediated through other factors.

* studies in in vitro systems designed to identify and purify the factors that actually have direct action on bone.

* studies of synergism and antagonism among bone active hormones and cytokines.

These areas of interest are not listed in any order or priority. They are only suggested examples of areas of research. Applicants are encouraged to propose other areas which are related to the objectives and scope described above.

MECHANISM OF SUPPORT

Assignment of Applications

Upon receipt, applications will be reviewed by staff for their responsiveness to the objectives of the PA. If an application i s considered unresponsive, the applicant will be contacted and given an opportunity to withdraw the application

or to have it considered for the regular grant program of the NIH. If an application submitted in response to this PA is identical to a research grant application already submitted to the NIH for review, the applicant will be asked to withdraw the pending application before the new one is accepted. Simultaneous submission of identical applications will not be allowed.

Applications will be received by the NIH, Division of Research Grants (DRG), referred to an appropriate Initial Review Group (IRG) for scientific merit review, and assigned to individual Institutes for possible funding. Referral decision will be governed by normal programmatic considerations as specified in the Referral Guidelines of the NIH, DRG. Some applications may receive dual assignment.

Review Procedures

Applications in response to this solicitation will be reviewed on a nationwide basis and in accord with the usual National Institutes of Health peer review procedures. Applications will first be reviewed for scientific and technical merit by an Initial Review Group composed primarily of non-federal scientific consultants, and then by the National Advisory Council of the appropriate Institute(s). The review criteria customarily employed by the National Institutes of Health for regular research grant applications will prevail.

Review Criteria

The factors to be considered in the evaluation of scientific merit of each application will be similar to those used in the review of traditional research project grant applications, including the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; the suitability of the facilities; and the appropriateness of the requested budget to the work proposed.

Format for Applications Applications should be submitted on form PHS 398, which is available from an applicant institution's Office of Sponsored Research or from the NIH Division of Research Grants (DRG). Use the conventional format for research project grant applications and ensure that the points identified in this PA in the section on "Review Procedures and Criteria" are fulfilled. To identify the application as a response to the PA, check "yes" on item two of page one of the application and enter the title "Research on Bone Active Hormones and Cytokines."

As in the case with regular research project grant applications, applicants are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project. However, except under very unusual circumstances, applications submitted in response to this solicitation should not request support for more than a three year period. At the end of the

initial award period, renewal applications may be submitted for further competitive review through the regular research grant program of the NIH.

Applications will be accepted in accordance with the announced receipt dates for new applications (see receipt dates and review schedule in application kits).

Application Procedure

The original and six copies of the application should be sent or delivered to:

Application Receipt Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, Maryland 20892

Inquiries

For further information, investigators are encourage to contact the following individuals:

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This program is described in the Catalog of Federal Domestic Assistance No. 13.846, Arthritis, Bone and Skin Diseases Research and No. 13.847, Diabetes, Endocrinology, and Metabolism, No. 13.855. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject of the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency Review.